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【 CASE REPORT 】

Successful Management of Hemosuccus Pancreaticus due to Pancreatic Adenocarcinoma by Chemoradiotherapy

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Abstract:
Management of hemosuccus pancreaticus (HP) due to pancreatic adenocarcinoma is problematic. This is the first report of the successful management of HP caused by pancreatic adenocarcinoma by chemoradiotherapy, which is a treatment option for cases with a high surgical risk that are not suitable for interventional radiology. In the present case, bloody pancreatic juice was detected in the main pancreatic duct, and anemia worsened without repeated blood transfusions. The patient ultimately underwent chemoradiotherapy comprising radiation of 3 Gy in 15 fractions concomitant with systemic chemotherapy of S-1. After the treatments, the anemia improved, and the patient was discharged on day 45.

Key words: pancreatic cancer, chemoradiotherapy, hemosuccus pancreaticus, bleeding

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Introduction

Hemosuccus pancreaticus (HP) involves bleeding from the papilla of Vater into the duodenum through the pancreatic duct. Management of HP depends on the underlying cause, and surgery or interventional radiology for selective arterial embolization is indicated in most cases. However, it is difficult to manage patients with a high surgical risk that are not suitable for interventional radiology or those with HP without vascular malformations.

We herein report a case of HP caused by pancreatic head carcinoma with multiple liver metastases treated with chemoradiotherapy (CRT). Surgery is the standard therapy for tumor-associated bleeding, but this case had unresectable metastasis. CRT may be a treatment option for patients with a high surgical risk who are unsuited for interventional radiology.

Case Report

A 67-year-old woman was admitted to our hospital complaining of epigastralgia. Her medical history included hypertension and osteoporosis, and she had no notable family medical history, smoking history, or drinking history.

She visited a nearby hospital with the chief complaint of epigastralgia, and upper gastrointestinal endoscopy revealed hemorrhaging from the papilla of Vater. Abdominal ultrasonography revealed a mass in the head of the pancreas and multiple masses in the liver. The patient was referred to our hospital for further investigation.

The presenting details were height, 146.1 cm; weight, 57.5 kg, body mass index, 26.9 kg/m^2; blood pressure, 131/73 mmHg; pulse, 72 beats/min; temperature, 36.4℃; and performance status, 1. Anemia was recognized in the palpebral conjunctiva. Microcytic-hypochromic anemia and slightly elevated biliary enzyme levels were found at the first visit. In addition, there was no abnormality in the coagulation system, and the levels of tumor markers were

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Table 1. Laboratory Data.

Complete blood count		Biochemistry			
WBC	6,500 /μL	TP	7.3 g/dL	CRP	0.70 mg/dL
Hb	7.2 g/dL	Alb	4.2 g/dL	HbA1c	7.4 %
MCV	78.3 fL	T-Bil	0.4 mg/dL		
MCHC	32.1 %	D-Bil	0.1 mg/dL	CEA	2 ng/mL
PLT	44.7×10^4 /μL	AST	25 IU/L	CA19-9	1 U/mL
Coagulation		ALT	21 IU/L	Span-1	≤10.0 U/mL
PT-INR	0.98	ALP	336 IU/L	DUPAN-2	132 U/mL
APTT	30.6 s	γ–GTP	138 IU/L		
		LDH	202 IU/L		
		AMY	71 IU/L		
		BUN	13.3 mg/dL		
		Cr	0.18 mg/dL		
		Na	142 mEq/L		
		K	3.9 mEq/L		
		Cl	104 mEq/L		

WBC: white blood cell, Hb: hemoglobin, MCV: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, PLT: platelet, PT-INR: prothrombin time-international normalized ratio, APTT: activated partial thromboplastin time, TP: total protain, Alb: albumin, T-Bil: total bilirubin, D-Bil: direct bilirubin, AST: asparatate aminotransferase, ALT: alanine aminotransferase, ALP: alkali-phosphatase, γ-GTP: γ-glutamyl transpeptidase, LDH: lactate dehydrogenase, AMY: amylase, BUN: blood urea nitrogen, Cr: creatinine, Na: natrium, K: kalium, Cl: chlorine, CRP: C-reactive protein, HbA1c: hemoglobin A1c, CEA: carcinoembryonic antigen, CA19-9: carbohydrate antigen 19-9, Span-1: s-pancreas-1 antigen, DUPAN-2: duke pancreatic monoclonal antigen type 2

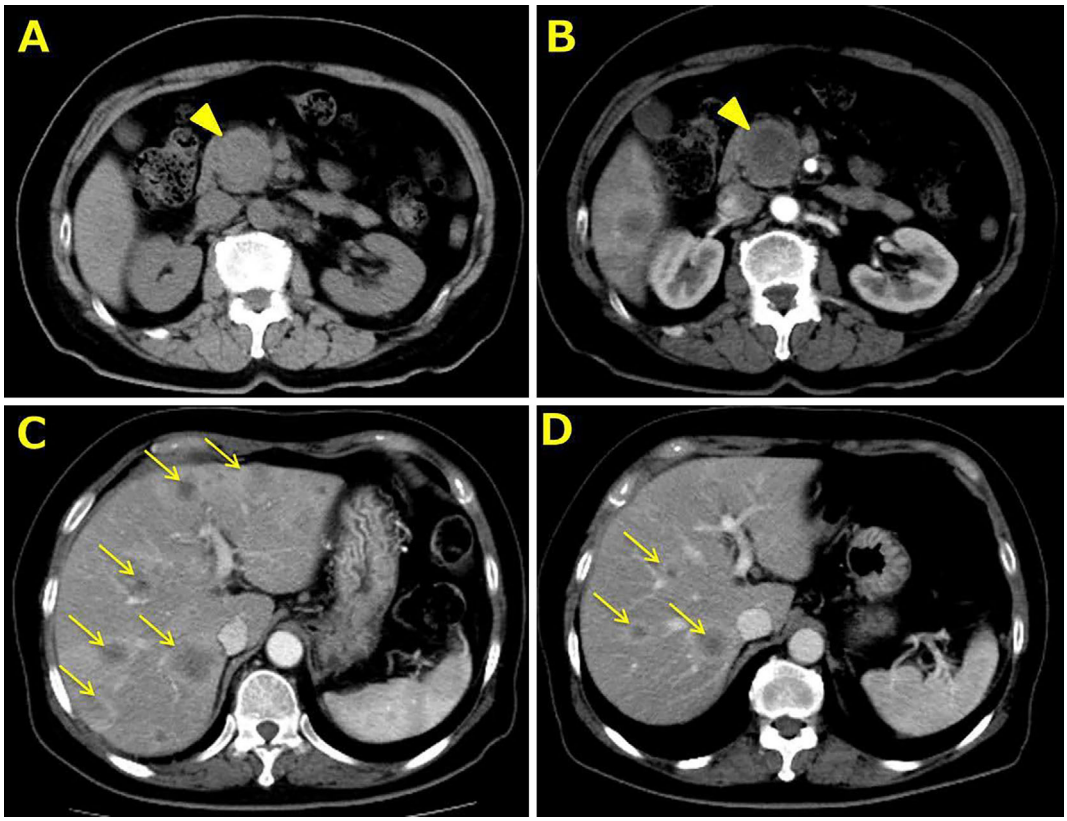

Figure 1. Intravenous contrast-enhanced computed tomography of the abdomen at the time of the diagnosis of pancreatic carcinoma (A, plain; B, arterial phase; C/D, portal phase). A low-density mass was detected in the head of the pancreas (A/B, arrowhead). Low-density masses in the liver were recognized as multiple metastases (C/D, arrow).

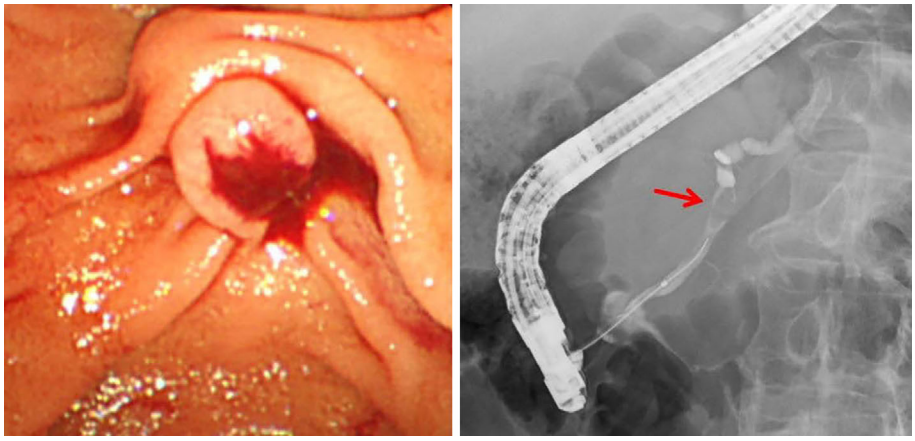

Figure 2. **Upper gastrointestinal endoscopy showed opening of and hemorrhaging from the papilla of Vater on initial view. Endoscopic retrograde pancreatography showed a partial defect of main pancreatic duct due to clots (arrow).**

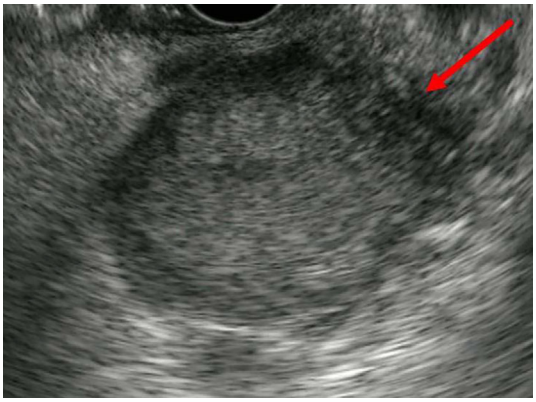

Figure 3. **EUS showed a 35×34-mm low-echoic mass on the head of the pancreas (arrow). EUS: endoscopic ultrasound**

within the normal ranges (Table 1). Abdominal computed tomography (CT) showed a 40-mm mass lesion in the head of the pancreas. In the arterial and portal venous phases, the pancreatic head tumor was poorly enhanced and had invaded surrounding tissue. In both lobes of the liver, numerous low-density areas with ring enhancement were detected. However, aneurysm around the pancreas and extravasation in the main pancreatic duct and digestive tract were not observed (Fig. 1). An upper gastrointestinal endoscopy revealed bloody discharge from the papilla of Vater. Blood clots were detected by endoscopic retrograde pancreatography as filling defects, and bloody pancreatic juice was aspirated (Fig. 2). Endoscopic ultrasound (EUS) revealed a hypoechoic tumor with a well-defined border, 35×34 mm in size, at the head of the pancreas (Fig. 3). Subsequently, EUS-guided fine-needle aspiration was performed, and the obtained specimens were diagnosed as poorly differentiated adenocarcinoma by hematoxylin and eosin staining and based on their diffuse positivity of CK7 and p53 by immunohistochemistry (Fig. 4). Therefore, the tumor was diagnosed as stage IV pancreatic head adenocarcinoma with liver metastasis according to the Union for International Cancer Control of Pancreatic Cancer (8th edition). The cause of HP was considered pancreatic head carcinoma.

An interventional radiological approach for HP was not indicated because no aneurysm was detected by contrast-enhanced CT. Anti-tumor therapy was considered for the treatment of HP; on day 3, nab-paclitaxel plus gemcitabine therapy was started. Because tarry stool and decreased hemoglobin were observed, a 6-French nasopancreatic drainage tube was placed close to the tumor on day 14 to monitor the hemorrhaging. Bloody pancreatic juice was continuously flowing out, and blood transfusion was frequently required to prevent the anemia from worsening. Abdominal angiography was performed on day 21 because of poor control of the bleeding by stent compression, but no arterial bleeding was detected on angiography (Fig. 5). Next, radiotherapy (3 Gy in 15 fractions) was given to manage the bleeding from the pancreatic head tumor on day 22. In addition, S-1 was indicated from day 29 because CRT with nab-paclitaxel plus gemcitabine was not established at that time. On day 38 (10 days after the start of radiotherapy), the pancreatic juice from the nasopancreatic tube had become pale, and no further blood transfusion was required (Fig. 6). There were no major complications during CRT, and the patient was discharged on day 45 (Fig. 7).

Discussion

The clinical entity of HP, involving bleeding from the papilla of Vater to the duodenum through the pancreatic duct, was first described by Lower and Farrell in a report of bleeding caused by a splenic artery aneurysm in 1931 (1). Pseudoaneurysm originating from the peripancreatic vessels is a main cause of hemorrhaging involving rupture into the pancreatic duct or a pancreatic cyst connected to the pancreatic duct in the background of chronic pancreatitis. Other causes include malignancies and vascular malformations. In HP associated with pancreatic tumors, the tumors invading the pancreatic duct produce intratumoral hemorrhaging, and

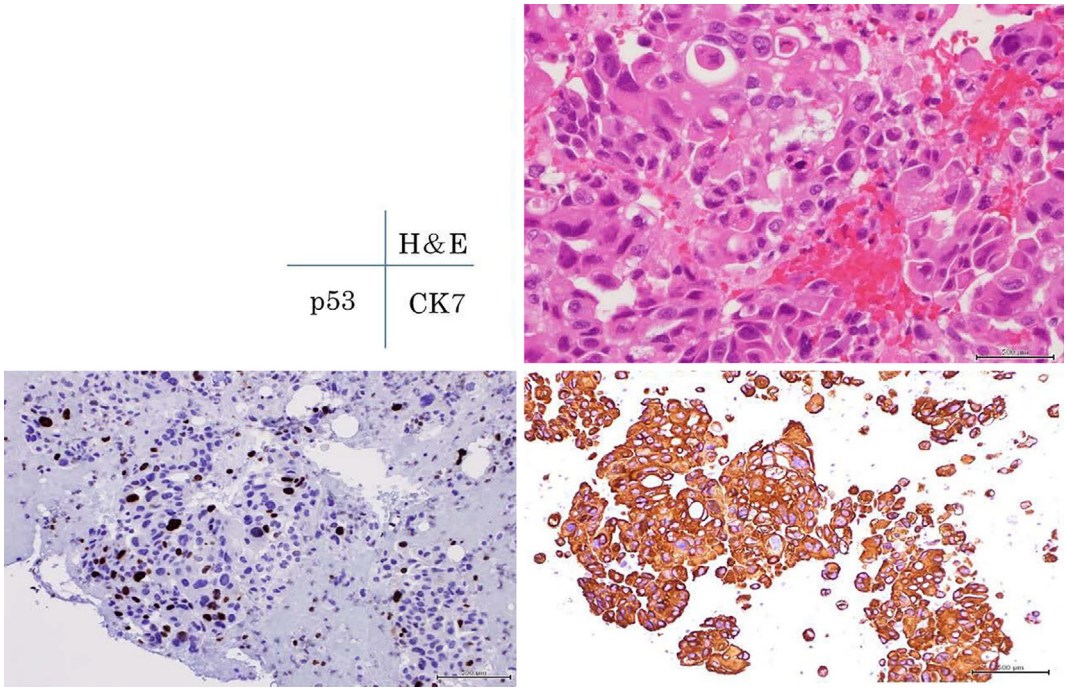

Figure 4. **EUS-guided fine-needle aspiration histopathology showed poorly differentiated adenocarcinoma. Immunostaining revealed diffuse expression of p53 and CK7. EUS: endoscopic ultrasound**

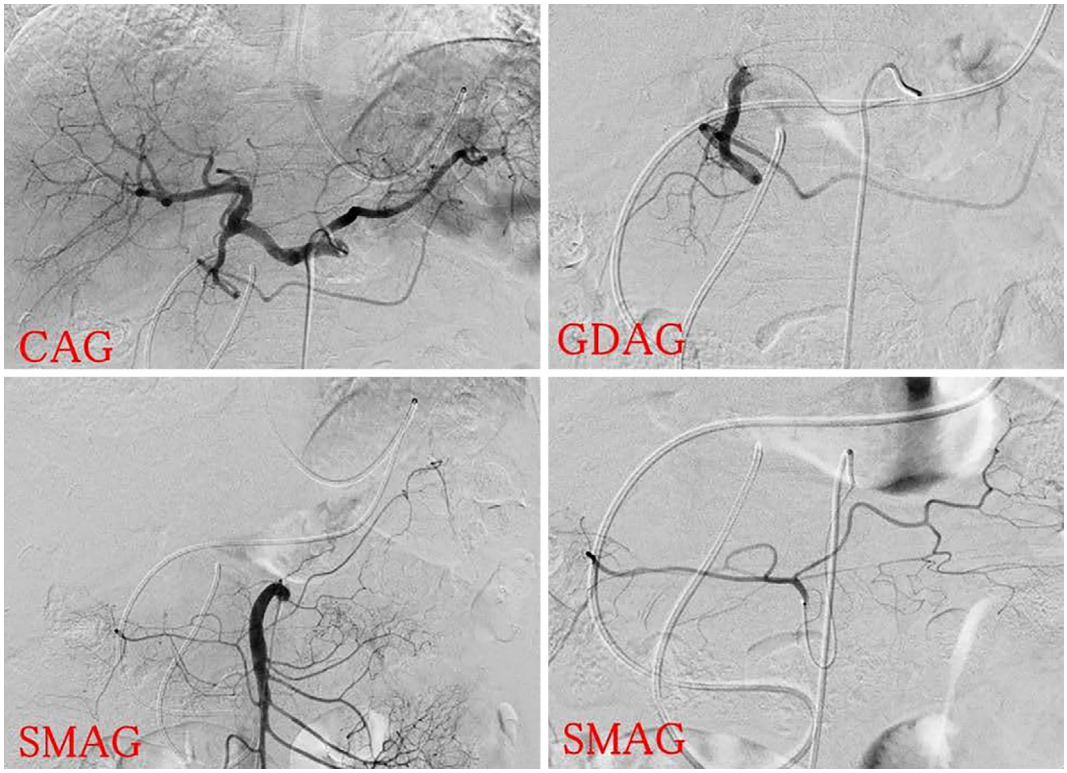

Figure 5. **Celiac trunk angiography (CAG), gastroduodenal angiography (GDAG), and superior mesenteric angiography (SMAG) showed no aneurysm or extravasation.**

tumor self-destruction causes rupture of the tumor blood vessels (2). The most common symptom is intermittent upper gastrointestinal bleeding, but epigastric pain associated with increased intraductal pressure due to clots is also reported (3). The diagnosis was confirmed by the detection of hemorrhaging from the papilla of Vater by upper gastrointestinal endoscopy. Interventional radiology and surgery are the most common treatments. As a new treatment, EUS-guided angiotherapy for bleeding pseudoaneurysm causing HP was first reported by Will et al. (4).

Figure 6. **The endoscopic nasopancreatic drainage fluid had become pale by day 38.**

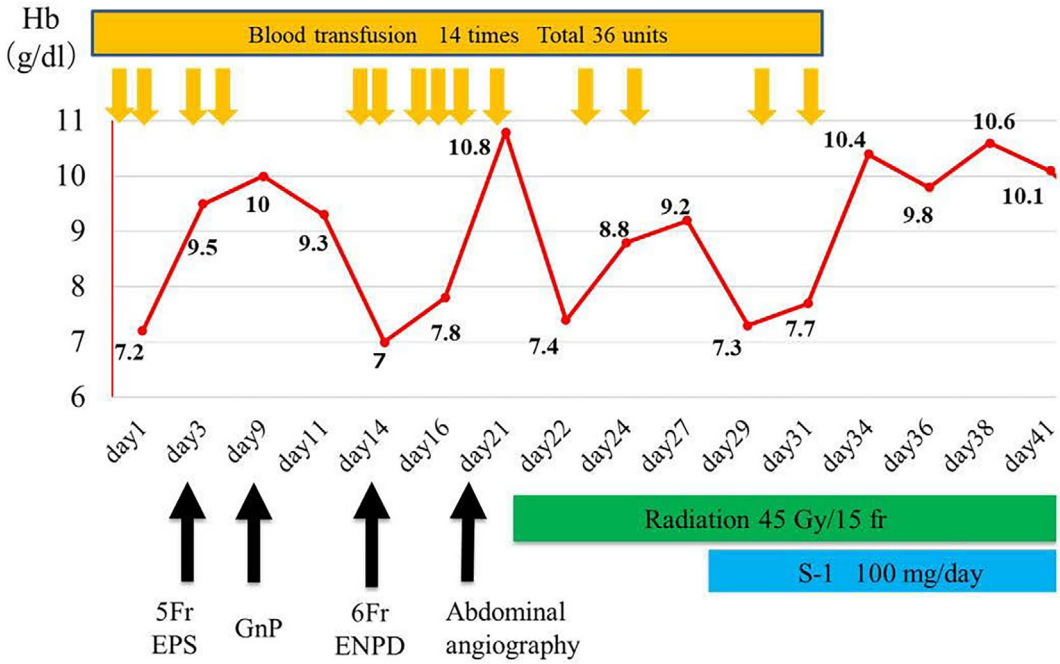

Figure 7. **Clinical course. EPS: endoscopic pancreatic stenting, ENPD: endoscopic nasopancreatic drainage**

A keyword search for 'hemosuccus pancreaticus' in PubMed between 1977 and 2018 yielded 161 reports. Middle-aged men with a history of alcohol abuse have multiple risk factors, and chronic pancreatitis is presumed to be an underlying disease, with pseudoaneurysm and cyst potentially occurring in the setting of inflammation. However, 10 cases of hemorrhaging from tumors, similar to the present case, were found in PubMed using the keywords 'hemosuccus pancreaticus' and 'carcinoma' (Table 2) (5-14). In particular, neoplastic HP is frequently reported in undifferentiated carcinoma, anaplastic pancreatic carcinoma, and vascular-rich tumors.

Although CRT for locally advanced pancreatic carcinoma has been reported (15-17), there are no reports of CRT as an effective treatment for hemostasis for HP due to pancreatic carcinoma. Three-dimensional conformal radiation therapy or intensity-modulated radiation therapy with a total dose of 50-54 Gy at 1.8-2 Gy per fraction is recommended for locally advanced pancreatic carcinoma (17). For gastric carcinoma, Asakura et al. reported that radiotherapy of 30 Gy in 10 fractions was efficacious and safe for preventing bleeding (18). In the present case, we chose a single dose of 3 Gy for hemostasis and applied a total of 45 Gy for local tumor control. The drainage from the nasopancreatic tube had become pale by 10 days after the initiation of RT. We consider this case to have responded to treatment, according to a retrospective cohort study of 17 cases of gastric cancer, in which hemostasis typically responded within 2 days (19).

Table 2. Reported Cases with the Key Words 'hemosuccus Pancreaticus' and 'carcinoma' (English Literature, 1997-2018).

	Age, Sex	Chief complaint	Kind of pancreatic disease	Location	Past history	Treatment	References
1	52, M	Melena	Metastatic pancreatic tumor of RCC	Tail	-	Total pancreatectomy	4
2	93, M	Anemia	Metastatic pancreatic tumor of RCC	Head	-	BSC	5
3	72, F	No symptom	MD-IPMC	Head	-	PD	6
4	71, F	Anemia	MCN	Tail	-	DP	7
5	77, F	Dilatation of MPD	PC (Carcinoma in situ)	Head	Pancreatitis	PD	8
6	78, M	Melena	MD-IPMN	Tail	Cerebral infarction	DP	9
7	79, M	Anemia	PC (stage III)	Head	-	FCSEMS+GEM	10
8	51, M	Jaundice	PC (stage III)	Head	-	PD	11
9	35, F	Aware of tumor	Serous cystic neoplasm	Whole	Hemangioblastomas of cerebellum	Total pancreatectomy	12
10	68, M	Melena	PC (anaplastic carcinoma)	Body, Tail	Diabetes	DP	13

RCC: renal cell carcinoma, BSC: best supportive care, MD-IPMN: main-duct intraductal papillary mucinous neoplasm, PD: pancreaticoduodenectomy, MCN: mucinous cystic neoplasm, DP: distal pancreatectomy, PC: pancreas carcinoma, FCSEMS: fully covered self-expanding metal stent, GEM: gemcitabine

Platelet aggregation occurs three minutes after radiotherapy, and coagulation activity is assumed to continue for seven days (20, 21). The effects of radiotherapy may support the early hemostatic response and be sustained for a re-bleeding-free survival of 27 days (19). Regarding the relationship between the tumor size and hemostasis, the tumor is not always shrunk in size on CT when the bleeding stopped because the tumor replaced post-CRT fibrosis as soft-tissue shadow on CT. Sa Cunha et al. reported that the evaluation of post-CRT re-staging on CT is inaccurate, and radical resection may be possible (22). We also temporarily controlled the tumor viability despite no effect on the tumor size. CRT may be a temporary treatment, and if the patient's condition permits it, surgery should be chosen for the hemostasis. Pancreatic cancer sometimes shows gastrointestinal bleeding due to tumor self-destruction, for which CRT is effective.

Conclusion

We experienced a case of pancreatic ductal bleeding associated with pancreatic head carcinoma that was successfully treated by CRT. This is the first report of HP in which hemostasis was achieved by CRT. Further cases need to be gathered to determine whether or not CRT is a viable alternative treatment for cases in which surgery and interventional radiology are not feasible.

The authors state that they have no Conflict of Interest (COI).

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